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Pharmaceuticals, Inc.

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Docket No. 99D-1454
Comments on Draft Guidance for Industry on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products, Chemistry, Manufacturing and Controls Documentation

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Dear Sir or Madam:

Boehringer Ingelheim Pharmaceuticals, Inc. is hereby submitting comments on the subject draft Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products, Chemistry, Manufacturing and Controls Documentation. We appreciate the opportunity to provide input on this guidance.

Please contact the undersigned if there are any questions on the attached commentary.

Sincerely,

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Attachment (29 pages)

99D-1454

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COMMENTS
Guidance for Industry
Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products
Chemistry, Manufacturing, and' Controls Documentation
DRAFT GUIDANCE

GENERAL COMMENTS

Asthma and COPD are among the most serious chronic and life-threatening diseases affecting Americans. An estimated 14.6 million Americans suffer from asthma and an additional 16.0 million are affected by chronic obstructive pulmonary disease (COPD). [American Lung Association http://www.lungusa.org/] Public attention has recently focused on these respiratory conditions because the prevalence and mortality have increased over the last decade. Asthma and COPD are often severe in nature and fatal if not properly treated. In addition, millions of Americans suffer from rhinitis, allergies, and the common cold.

Inhalation solutions and suspensions are an essential means of delivering doses of medication to the lungs of asthma and COPD patients often on a daily basis. Likewise, nasal sprays are the most common means of delivering medication to the nasal passages of patients suffering from rhinitis and the nasal symptoms of allergies and colds. Millions of patients depend on these medications and drug delivery options for the effective treatment of respiratory and nasal diseases.

The pharmaceutical industry and FDA have an enormous responsibility to respond to the needs of patients for nasal and pulmonary solution medications by expediting new products to the market while maintaining appropriate standards of safety, efficacy, and quality. FDA and the Pulmonary Division are commended on their efforts over the past years to ensure the safety, efficacy, and quality of nasal and inhalation solution medications. In particular, the efforts of the CMC regulators have supported the implementation of quality standards and process technologies which ensure that these products are reliable and consistent so far as their physical properties and-performance. The Agency is also commended for publishing this Guidance for Industry as an aid to facilitate the approval of new nasal and respiratory solution / suspension products.

The Industry has been concerned over incremental changes in *de facto* regulatory requirements created by the Agency during the review cycles of New Drug Applications. We share the Agency's concern regarding the quality of nasal and inhalation products, and believe that the Pulmonary Division has requested tight product controls in good faith. This DRAFT Guidance for Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products, coupled with recent draft guidance for MDIs/DPIs and Bioequivalence, provides valuable information to assist developers of these products more clearly understand the Agency's expectations.

The Agency took an important step toward addressing the CMC issues for MDI and DPI delivery systems in the **AAPS Workshop on Regulatory Issues Related to Drug Products for Oral Inhalation and Nasal Delivery Co-Sponsored with FDA and USP,** June 3-4, 1999, Washington, DC. Since the Guidance for Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products was posted on June 2, it was, however, not possible to have' a meaningful review of the issues specific to the nasal and solution / suspension dosage'forms at the time of the Workshop. Boehringer Ingelheim would strongly recommend and offer to participate in an on-going workshop process to address a number of the science, technology; and quality control issues that are critical to the future of MDI, DPI, nasal and solution/suspension 'products.

Boehringer Ingelheim appreciates the opportunity to comment on this important new draft Guidance. We have several general comments which are provided below, followed by a number of specific comments in the next section of this document, which are cross-referenced to the section and lines of the draft Guidance. As with the MDI / DPI Guidance, this Guidance is of critical importance to process of approving new inhalation and nasal medications. We would ask that the Agency consider utilizing technical workshops with industry, academia, and pharmacopoeia experts to recommend revisions and to prepare a REVISED DRAFT for review and comment.

A major concern is that this Guidance confuses the approval of nebulizers as Class II medical devices by CDRH with the approval of Inhalation Solution drug products by the Pulmonary Division. The Guidance attempts to treat a "specified" nebulizer as part of the drug product, but nebulizers and Inhalation Solutions are made by different companies and approved by different divisions of FDA. The Guidance neither provides nor sites scientific reports to justify this requirement nor does it explain why the "equivalency" requirement of CDRH 5 10K Application is inadequate to ensure consistent performance across the approved nebulizer products. The Guidance should be revised to remove the requirement of a "specified nebulizer" from the product labeling.

As with the MDI/DPI Guidance, this Guidance is isolated from the thinking and recommendations of external sources of aerosol and quality control expertise. In recent years, ICH and other bodies have worked to create approaches to product quality which utilize the experience and expertise of scientists working in the field to develop internationally accepted quality criteria. This Guidance does not reflect the concepts brought forth by these consensus processes.

For example, the Guidance selectively applies portions of the ICH Guidelines and contradicts other portions. In line 347 is a reference ***to Q2A Text on Validation of Analytical Procedures*** and ***Q2B Validation of Analytical Procedures: Methodology.*** In line 13 13 is a reference to ***Q1B Photostability Testing of New Drug Substances and Products.*** Conspicuously absent are ICH concepts related to impurities, stability and specifications embodied in the guidelines ***Q3B Impurities in New Drug Products, Q1A Stability Testing of New Drug Substances and Products*** and ***Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.*** While ICH guidelines do not address the unique technologies

required for nasal and inhalation solutions / suspensions, these guidelines are widely accepted and could provide a robust framework for the manufacturing controls that are generally applicable to drug substances and drug products. The FDA Guidance should be revised to incorporate ICH guidelines where possible and provide justification in cases where tighter or more extensive controls are required.

The Guidance is conspicuously silent on the subject of criteria for setting specifications. This topic is critical to the submission and approval of an NDA, and has been the cause of considerable debate and disagreement between the industry and FDA. It is also the subject of a'widely accepted ICH draft guideline, *Q6A* . ***Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.*** Past experience with the Division is unsatisfactory with respect to the demands to set "tighter specifications" based on a non-statistical approach to high and low values and individual judgments about outlier test results.

The Guidance makes repeated reference to concepts of "product consistency" and "future batch-to-batch consistency" and "reproducibility". However, no information is given to allow a quantitative or numerical approach to defining "consistent" or to determine when "reproducibility" has been violated. We contrast this omission with the discussion of statistical techniques (with references) given in the FDA draft guideline for Stability Testing. Suitable approaches that are applicable to nasal and solution / suspension inhalation products are well accepted in the fields of process and quality control and should be adopted by FDA. The Guidance should be amended to address in detail the use of scientifically recognized statistical and other quality control concepts and procedures to determine specifications.

The Agency has taken an approach to container closure systems which is unsupported by published scientific information and inconsistent with current concepts regarding the control of the quality of manufactured products. The Agency posted (July 1999) the final ***Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION.*** This Guidance addresses **Inhalation Drug Products as follows:**

> ***Inhalation drug products include inhalation aerosols (metered dose inhalers); inhalation solutions, suspensions, and sprays (administered via nebulizers); inhalation powders (dry powder inhalers); and nasal sprays. The CMC and preclinical considerations for inhalation drug products are unique in that these drug products are intended for respiratory-tract compromised patients. This is reflected in the level of concern given to the nature of the packaging components that may come in contact with the dosage form or the patient (see Table 1). Guidance regarding the container closure system information to support the approval of applications for inhalation drug products will be provided in two guidance documents when finalized: the guidance***

for industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products; Chemistry, Manufacturing and Controls Documentation (a draft was issued in October 1998), and the guidance for industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; 'Chemistry, Manufacturing and Controls Documentation, which is currently under development,

One of the implications of this statement-is that the lungs are more sensitive to chemicals, potentially derived from inhalation product packaging components than the organs of the body that are exposed by drug solutions that are administered by injection. This claim by FDA is to our knowledge not supported by published reports or clinical or pre-clinical safety studies. The claim is also contradicted in the cited Table 1 of the Container Closure Guidance where inhalation aerosols and solutions, injections, and injectable suspensions have the same assessment of "packaging concerns".

One of the fundamental concepts of quality control is to build quality into the product by careful management and testing of components and materials. Quality begins with developing a complete understanding of the materials and components during development, and to that end BI supports the forms of chemical and physical characterization during development as proposed by the Guidance. The development data form the basis for a case-by-case assessment of the need for specific controls of the materials and components at the appropriate point in the supply chain.

However, universal requirements to control the same parameters in materials, sub-components (parts), components, and the finished product, as required by the Container Closure section of the ***Draft*** **Guidance** ***for Industry Nasal Spray and Inhalation Solution, Suspension, and*** Spray Drug ***Products***, fail to recognize the state-of-the-art in quality systems and the Agency's own GMP systems for supplier quality. The Agency is requested to reconsider the practice attempting to control the quality chain by over-testing manufactured components and finished products.

The highest level of container closure control. as described,,@ the Final Container Closure Guidance has been accepted as suitable for injection products and should be adopted for inhalation products. Any lingering concerns about the supply chain of raw materials (polymers, resins, etc.), parts, and components as delivered to the pharmaceutical production facilities should be addressed as a GMP supplier quality issue.

Possibly the greatest concern is that the Guidance attempts to-justify CMC controls for nasal and solution / suspension inhalation products with unsupported statements

regarding special safety and efficacy requirements. To use the terminology of the FDA Division of Drug Marketing, Advertising and Communications (DDMAC), claims either implicit or explicit regarding clinical efficacy and safety are misleading. The fundamental principles of product registration are that preclinical and clinical studies demonstrate safety and efficacy, and that the CMC package demonstrates an appropriate level of consistency between the clinical test materials and the marketed product. The Guidance should be revised so as to replace the implications that control of certain CMC parameters is directly associated with clinical outcomes.

SPECIFIC COMMENTS

Section II. BACKGROUND Parts A, B and C
Lines 32-119

The relationship between CMC test parameters and clinical efficacy and safety is misleading and not supported by published studies. The Guidance should present a more balanced picture of the state of the art of the demonstrated relationships between ***in vivo*** and ***in vitro*** testing of nasal and inhalation products. CMC testing requirements can not be justified by or correlated to clinical efficacy and have yet to be established-as surrogates for clinical outcomes. The Guidance should be revised to recognize that while nasal and inhalation products control the dose delivered to the patient, ***in vitro*** tests are much more sensitive and discriminating than clinical endpoints in assessing delivery system performance.

Line 46
Please delete the phrase ***"as well as the product's efficacy"*** in the sentence: ***"These differences... can affect the ability of the product to deliver reproducible doses to patients over the life of the product as well as the product's efficacy."***

Section II.B. Inhalation Solutions and Suspensions
"Specified" Nebulizer(s)
Lines 71-72

"Inhalation solutions and suspensions are intendedfor delivery to the lungs by oral inhalation for local and/or systemic effects and are to be used with a specified nebulizer(s)."

The Guidance also requires a one time study to characterize the nebulizer (lines 1301-1305) and states that under the DESCRIPTION section the administration information will limit the use of the inhalation solution product to a specific nebulizer. {lines 1513-1515)

Nebulizers are medical devices developed, manufactured, and marketed by companies other than the drug product supplier. Nebulizers are Class II devices which are approved by the Center for Devices and Radiological Health, Office of Device Evaluation Division of Cardiovascular and Respiratory Devices. The current thinking of CDRH regarding

performance testing including ***in vitro/ in vivo,*** and clinical evaluations is presented in REVIEWER GUIDANCE FOR NEBULIZERS, METERED DOSE INHALERS, SPACERS AND ACTUATORS. This Guidance is clear on the point that nebulizers are regulated by CDRH.

> ***"'Also note the Intercenter Agreements define that an aerosol delivery device will be considered a drug product and regulated by the Center for Drug Evaluation and Research (CDER), when the primary purpose of the device is delivering or aiding in the delivery of a drug and the device is distributed with the drug. Therefore, if a device is intended to deliver a specific drug or if the labeling references a specific drug product, the device will be considered a drug product and regulated by CDER. It is important to note that Metered Dose Inhalers and Actuators are reviewed in the Centerfor Drug Evaluation and Research (CDER), where Nebulizers and Spacers as well as Metered Dose Inhalers intended for a ventilator circuit are reviewed in the Centerfor Devices and Radiological Health (CDRH)."***

The CDRH guidance is clear that the review process for 510(k) premarket notifications is intended to ensure that nebulizers and other devices are safe and effective.

> ***"This reviewer guidance document suggests the importance of environmental testing, performance evaluations, and labeling information for aerosol delivery devices."***
>
> ***"The in vitro performance section of the premarket notification must detail adequate protocols and bench testing procedures which demonstrates equivalency of the subject aerosol delivery system and the predicate device,"***
>
> ***"For each aerosol delivery device or accessory such as an add-on spacer device, particle size distribution testing must include testing with at least one bronchodilator and one steroid. Particle size distribution testing must include at least three different drugs consisting of bronchodilators, steroids, antiallergics, mucokinetic agents, or antiviral agents."***

The CDER Guidance for Nasal / Solution / Suspension products is not clear on the procedure or rationale for conducting ***in vitro*** nebulizer studies on a product by product basis and identifying specific nebulizer(s) as part of the drug product labeling. Note that the CDRH Guidance requires that a nebulizer demonstrate "equivalency" with at least two pharmacological classes and three specific drug product particle size distributions. The Agency should avoid the promulgation of confusing and overlapping Guidances and not attempt to incorporate approval and control procedures for nebuiizers in an ***ad hoc*** manner into the NDA for Inhalation Solution products. The CDER Guidance should be revised to recognize and to cross-reference the CDRH Guidance for the regulation of nebulizers used to deliver solution drug products.

Section II.C. Inhalation Sprays
Lines SO-81

It would be helpful for the Guideline to provide additional clarification on the difference between an inhalation solution and an inhalation spray. It appears that the key difference is that an inhalation solution is administered using an external device; and an inhalation spray consists of the formulation and the container closure system, of which the delivery device is an integral part.

Lines 102-108
Please delete the section: ***"Regardless of the design, the most crucial attributes are the reproducibility of the dose, the spray plume, and the particle/droplet size distribution, since these parameters directly affect the delivery of the drug substance to the intended biological target. Maintaining the reproducibility of these parameters through the expiration dating period and.. . through its lifetime under patient-use conditions will probably present the most formidable challenges."***

Clinical trials with some of the most commonly used inhalation products have demonstrated that chemical and physical testing is much more sensitive to changes in the drug product than are the clinical measures of the respiratory performance of patients: For example, dosing studies may demonstrate that patients are on the plateau of the dose response curve and insensitive to the dose of the drug. Consideration of drug product parameters in a clinical study should be specific to the drug product and the ability of clinical assessment to discriminate such effects. It is not appropriate to generalize that CMC controls of product performance are justified on the basis of clinical outcomes.

Studies of spray pattern and plume geometry are appropriate for early product development studies to determine the appropriate valve and mouthpiece design. Control of the components with appropriate sampling plans and dimensional measurements is far more precise than measuring the spray plume reproducibility. (See the comments for section III.F. 1 .i.) Spray pattern and plume geometry measurements are redundant and generally ineffective procedures to control component parameters.

Product Performance Under Patient-Use Conditions
Line 105-108

Products are designed to minimize the potential for misuse or abuse. Control procedures and specifications can support the use of the product as described in the product labeling and instructions to patient, but can neither anticipate nor control for parameters related to possible product misuse or abuse.

Section III.B. - Composition
Lines 141-142

"Similarly, a production batch formula representative of the one to be employed in the manufacture of the drug product should be included."

We recommend that a production batch formula not be presented as part of the Composition section of the NDA, but rather be presented together with the information on the Method of Manufacture (see Section III.E of the draft Guidance). The production batch formula is more readily understood in the context of the manufacturing process, particularly for multi-stage products where the batch formula may be separated into batch formulae for manufacturing intermediates. Placing the manufacturing batch formula in the section on Method of Manufacture is consistent with the draft ICH Guideline M4 ***The Common Technical Document,*** which has the batch formula located with the method of manufacture.

Lines 142-145

We understand the word "excess" used in these lines to be synonymous with "overage". We suggest that the word be changed to "overage" to be consistent with other FDA Guidelines.

Lines 145147

"Any intended change in the formulation from that used in the submitted batches (e.g., clinical, biobatch, primary stability, production) should be clearly indicated. "

This sentence is not clear. We infer that FDA wants the NDA to describe any differences in the proposed commercial formulation versus that of the biobatch, primary stability batches, etc. Therefore, we suggest that Section III.B Composition, be subdivided into III.B. 1 Composition of the Commercial Product and III.B.2 Clinical Trial Formulations. Section III.B.2 could present the formulations of the biobatch, primary stability, etc., if different from the proposed commercial formulation.

This would be consistent with the draft ICH Guideline ***M4 Common Technical Document,*** which has two sections, ***i.e.,*** "Composition" and "Investigational Formula(e)".

Lines 149-157

We suggest that the guidance in this paragraph be moved to Section IV of the draft Guidance. The advice being given in these lines appears to relate to issues that should be addressed by pharmaceutical and packaging development studies.

Section III.C.l. - Active Ingredients
Lines 163-169

"Information regarding the comprehensive characterization of the physical and chemical properties of the drug substance should be included in the application...."

Developmental studies are necessary to determine the important physico-chemical properties of the drug substance as they potentially affect stability, the ability to

manufacture, and bioavailability. Not all the physico-chemical properties determined in developmental work need to be controlled by formal specifications. The Guidance should reference (and/or incorporate) the Decision Trees in the ICH Q6A guideline ***Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products; Chemical Substances*** as rationale for determining if specifications should be set.

Also, for your information, the USP Division of Standards Development Subcommittee on Excipients-Methods and the Advisory Panel on Physical Test Methods are developing monograph test methods for optical microscopy <776> to measure particle shape and size, powder fineness <811> for particle size distribution, specific surface area <846>, density of solids <699>, bulk and tapped density <616> and crystal forms.

Appropriate Acceptance Criteria and Tests
Microbial Limits
Line 175-176

For synthetic drug substances, microbial limits is considered a GMP issue. In the justification of specifications, a one time study should be provided to show no growth of a panel of aerobic organisms and common pathogens to support deletion of this release test. A commitment may be provided to conducting a microbial burden test annual as part of supplier qualification.

Line 176
Melting Range

Typically melting point testing is only done to characterize the drug substance in the physico-chemical Section of the NDA. Purity is controlled by the purity test. Polymorphic forms if present are controlled either by IR or X-ray and then only if they affect stability or bioavailabilty per *ICH Q6A* Decision Tree #4.

Surface Area, Crystal Form(s)
Line 176-177

USP test methods are under development but have not yet been finalized for specific surface area and crystal form(s). Please delete these tests from the specifications.

"Crystalline forms (e.g., shape, surface texture) of the drug substance.. ."
Line 181-182

No good measurement of particle texture in a powder system has been published in the literature. The words "surface texture" should be omitted from the guideline until a robust method is available or clarification of the term "surface texture" is necessary. Descriptors of crystal shape are qualitative, and measurement of a meaningful change would be a challenge. The USP monograph on crystalline forms has not been adopted as yet. The value of control of crystalline forms, polymorphic forms, is again dependent on

its affect on stability or bioavailability. Reference should be made to Decision Tree #4 in *ICH Q6A* for the studies required to justify the deletion of this test for suspension formulations.

Amorphous Content
Line 188-190

We recommend that a specification for amorphous content should only be required if development studies show that its control is necessary for the performance of the drug product.

Purity
Lines 193-196

We suggest that the sentence be re-worded to read ***"Important impurity-related parameters may include organic volatile impurities and/or residual solvents, organic impurities (synthesis-related and degradation products), and inorganic impurities (e.g., reagents, catalysts)."*** This wording would be more consistent with the terms for impurities used in ICH Guidelines *Q3A* and *Q3B*.

Lines 196-203

"Any recurring impurity found in the drug substance at a concentration of 0. I percent or greater, relative to the parent drug substance, should be identified and qualified".

The Guidance should be revised for consistency with the qualification threshold in the ***ICH Q3A*** guideline ***Impurities in New Drug Substances,*** which states: "data may be needed when the usual qualification threshold limits below are exceeded:

Maximum Daily Dose	Qualification Threshold
≤ 2 g/day	0.1% or 1 mg per day intake **(whichever is lower)**
> 2 g/day	0.05%

Higher or lower threshold limits for qualification of impurities may be appropriate.. ."

Also, the rationale for establishing impurity specifications should reference the *ICH Q6A* guideline.

Section III.C.2. - Excipients
Line 209-275

The first paragraph of this section states (line 212) that excipients for oral inhalation products should be "completely" characterized. The meaning of the term "completely" is unclear, and does not indicate the scientific basis for applying additional "strict quality controls".

A clear distinction is needed between the requirements proposed for critical excipients and those for non-critical excipients. For example, in the first paragraph an unclear phrase is "a similar level of control should be applied for excipients that have an effect on the suspension..." (line 214). It is recommended that the term "critical excipient" be defined in the Glossary, and that the wording of the entire section be clarified. (Example: in line 240 add the word "critical" excipient.)

Lines 228-230

We do not agree with the proposal that DMFs should be submitted for all noncompendial excipients. We concur that appropriate excipient specifications should be based on adequate characterization studies; and we suggest that a DMF is needed only for those excipients that are "novel" ***(i.e.,*** an excipient not contained in any drug product approved by FDA, not merely inhalation products) and for those excipients which are proprietary mixtures.

Lines 245-256

"If excipients are accepted based on certificates of analysis from the manufacturers with the applicant performing a specific identification test upon receipt, the applicant should also develop validated procedures or have access to all of the manufacturer's analytical and other test procedures to allow them to establish the reliability of the test results at appropriate intervals (21 CFR 21 I. 84). The applicant should confirm the supplier's results by testing (I) an adequate number of batches of each excipient used in preparing the submitted drug product batches (e.g., clinical, primary stability, biobatch, and production batches) and (2) a predetermined number of batches of each excipient used in preparing postapproval drug product batches. When excipients for suspension formulations play a critical role in the quality and performance of the drug product, multiple incoming batches of these excipients should be tested to confirm the supplier's test results."

We agree that a supplier's test results should be qualified prior to acceptance of supplier's COA results in lieu of full testing. However, we do not believe that the Guidance should specify what batch experience should be used to support supplier qualification beyond the provisions of 2 1 CFR 2 11.84 (see text below).

Once a supplier is both certified (compliant with GMPs) and qualified (for use in the drug product), there is no current GMP requirement to conduct full testing on a predetermined number of batches post approval.

21 CFR 211.84

(d) Samples shall be examined and tested as follows:

> ***(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.***
>
> ***(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be acceptedfrom the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided***

that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

(3) Containers and closures shall be tested for conformance with all appropriate written procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.

(4) When appropriate, components shall be microscopically examined.

(5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.

(6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and releasedfor use. Any lot of such material that does not meet such specifications shall be rejected.

Section III.D. - Manufacturers
Drug Product
Lines 279-284

We suggest that the requirement for a "building number" be limited to manufacturing facilities involved with the manufacture of a sterile product. This would be more consistent with the concept of "site" and "facility", as used in the FDA draft Guidance for Industry, *Changes to an Approved NDA or ANDA*, and the FDA draft Guidance for Industry, *Stability Testing of Drug Substances and Drug Products*.

With the requirement that inhalation solutions for nebulization be manufactured sterile (See FR 96N-0048, Vol. 62, No. 184, p. 49638, September 23, 1997), the manufacturer should be identified by filling room and filling line for which sterile process validation is required. Manufacturing approval is specific to those areas.

Excipients
Lines 284-285

"*Excipient manufacturers should be identified by name and address.*"

The source for compendial excipients has typically been-a compliance issue relevant to the qualification and certification of suppliers. The source of supply of compendial excipients should not be identified in the regulatory submission. We recommend that the Guidance be revised to delete this requirement except for novel excipients and proprietary mixtures.

Section III.E. – Method(s) of Manufacture and Packaging
Sterility
Lines 292-293

"All inhalation solutions, suspensions, and spray drug products should be manufactured as sterile products, and their sterility should be ensured through the expiration dating period."

Also **line** *68:* "***Inhalation solution and suspension drug products are sterile.. .***"
Also **line 81:** ***"The (inhalation spray) formulations are sterile..."***
Also lines 630-631: ***"All inhalation solutions, suspensions, and spray drug products should be sterile."***

The above statements are in conflict with the FR Notice 96N-0048, Vol. 62, No. 184, p. 49638, September 23, 1997, which applies only to the ***inhalation solutions*** dosage form. This FR notice specifically states: 'Inhalation solutions for nebulization, as the term is used in this document, refers to inhalation solutions administered as a fine aqueous mist created by an atomizer or nebulizer.' Nasal sprays are not included. Inhalation suspensions and spray drug products may be more like metered dose inhalers and-dry powder inhalers which are not required to be sterile. For instance, spray drug products compounded in ethanol as a vehicle are bactericidal. The Agency should clarify the sterility requirements by developing a decision criteria for the suspension and spray drug products based upon the route of administration and the ability of the formulation to support microbial growth.

Micronization
Line 297

"*. . . re-use* ***of carry-overs from previous micronized lots"***

The above phrase should be deleted. A batch may be divided into several sub-lots to meet the capacity of the micronizer. Re-use of carry-overs between lots but within one batch is a practice which is controlled under GMPs through validation. Each lot is tested to meet specifications prior to pooling.

Batch Records
Lines 304-306

"A copy of the actual (executed) batch record and in-process controls should be submitted, as appropriate, for representative batches (e.g., clinical, biobatch, primary stability, production)."

The proposed requirement for submission of executed batch records exceeds the current requirements at 2 1 CFR 3 14.50(d)(1)(ii)(b). The federal regulations state that executed batch records must be submitted for each batch of drug product used in a bioavailability/bioequivalence study (a batch commonly known as a "biobatch"), and

used in a primary stability study. The federal regulations do not include a requirement to submit "clinical" or "production" batches, and listing these batches in the draft Guidance is confusing. We suggest that the guideline cite the required executed batch records listed in the regulations at 21 CFR 314.50(d)(1)(ii)(b), and add that applicants should consult with the Division to determine if submission of any additional executed batch records (e.g., a representative batch used in a pivotal clinical trial) may be required.

Sealing
Lines 326-328

Please delete the phrase "***for seal completeness and for seal strength".*** There is a wide range of seal strength results which would provide acceptable barrier properties for a drug product. The acceptability of the sealing should be controlled in a limit test. Above the limit, a quantitative (seal strength) test would have no value and might not be feasible for routine control. We propose the sentence: ***"Appropriate integrity testing and acceptance criteria should be established to ensure acceptable sealing properties within a batch and among batches."***

Section III.F. - Specification of the Drug Product
Line 342-343

An "analytical sampling plan" is not mentioned in the draft ICH Guideline *Q6A* ***Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.*** We are aware that the concept of sampling plans is also currently under discussion in the development of the ICH Guideline M4 ***Common Technical Document.*** It has been suggested that sampling plans should be eliminated from the content of the common dossier. We believe that sampling plans should be considered an aspect of GMPs, and recommend that a requirement for sampling plans be deleted from this Guidance. A reference to "sampling plan" also appears in **Lines 861,995, and 1104,** where we recommend deletion.

Line 347

The Guidance requests documentation ***"in sufficient detail to permit validation by Agency laboratories".*** We suggest the phrase be replaced with "***. . . to permit verification...***"

Lines 348-349
"Comprehensive and well-defined in-vitro performance characteristics should be established before initiating critical clinical or bioequivalence studies. Appropriate, validated test procedures.. ."

The Guidance should refrain from addressing activities carried out during product development. The wording is inconsistent with other overlapping FDA DRAFT Guidance for Industry, ***INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry, Manufacturing, and Controls, Content and Format, February 1999.***

The drug product specification section of the Guidance should unambiguously pertain to the registration of drug product. We propose that lines 348-349 be replaced with the following:

"In phase 2 and in phase 3/pivotal studies, the container closure system should be similar to that intended for the marketed drug product. For registration appropriate, validated test procedures. . ."

Section III.F.1. -- Nasal Sprays

Section III.F.1.a -- Appearance, Color and Clarity
Line 360

Please delete the word "Clarity" in the title. The text of this paragraph does not provide any guidance on a Clarity test. Such a Clarity test has not been required in past Agency guidance, and no scientific rationale is provided for proposing it here.

Section III.F.1.b. - Identification
Lines 372-373

The Guidance should be revised to delete *"Chromatographic* ***retention time alone is not an adequate method . . ."***. It should be replaced with: ***"A single chromatographic procedure is not adequate to ensure the identity*** *of* ***the drug substance in the drug product. In addition to the chromatographic procedure, a second independent procedure should be applied (e.g. HPLC, TLC, UV-spectra*** *and/or* ***IR)."***

Section III.F.1.d. - Impurities and Degradation Products
Lines 391-393

"For identification and qualification thresholds, refer to the appropriate guidance. All related impurities appearing at levels *of* ***0.1 percent or greater should be specified."***

The Guidance makes an ambiguous statement about "the appropriate guidance" and does not specifically mention ICH Guidelines ***Q3B Impurities in New Drug Products*** and ***Q6A Specifications: Test Procedures and Acceptance Criteria*** *for* ***New Drug Substances and New Drug Products: Chemical Substances.*** These consensus ICI-I guidelines contain concepts regarding impurities and degradation products in drug products. The *Q3B* guideline states that ***"Impurities present in the new drug substance need not be monitored in drug products unless they are also degradation products."***

The Guidance appears to have set aside these consensus guidelines in favor of a statement that does not differentiate degradation products and process impurities. Drug substance process impurities are fully controlled by the specification and test methods for the drug substance. Including drug substance impurities in the drug product controls is redundant, confusing, and can at times compromise that quantitative testing technology so far as

controlling the drug product degradation products. The Guidance should be amended to remove drug substance process impurities from the drug product controls.

The new proposed requirement to specify all related impurities appearing at or above 0.1 percent should be deleted. We are aware that ***ICH Q3B*** proposed revisions are under discussion. These discussions include establishing a threshold above which individual degradation products must be specified. We recommend that this Guidance defer to the ICH decisions reached.

Section III.F.1.e – Preservatives(s) and Stabilizing Excipient(s) Assay

The reference in line 402 should be changed from "Refer to section III.F. 1 .o" to 'Refer to section IV.L".

Section III.F.1.f – Pump Delivery

Pump delivery is an important test criterion for pump components. Pump delivery of drug product is useful as a development tool and in investigations of out of specification dosing results. However, as a release or stability specification drug product pump delivery is a redundant control procedure and should not be used. The Guidance should be revised so as not to require redundant or overlapping control procedures.

Section III.F.1.g -Spray Content Uniformity (SCU)
Lines 433-447

Please delete the acceptance criteria 80-120 % (first tier) and 75-125 % (second tier), and apply the acceptance criteria of USP 23, Suppl. 10, General Chapters <601> and <905>, (i.e., **first tier: 75-125 %, second tier: 75-125 % and 65-135 % of label claim).**

Alternatively, the Guidance should be revised so as to provide a process for setting dose content uniformity specification that applies currently accepted statistical methods such as those used to establish the USP <905> criteria. Product uniformity specifications for new products should be determined by performance data as developed for the specific product, and not prescribed in an arbitrary manner or based on the data obtained for existing products.

The specification as presented is statistically flawed and is predicted to reject product in an arbitrary manner. The failure of the proposed criteria as an acceptable control specification is illustrated as follows:

> The sample size is 10 in the first tier. In the event that there is more than one value in the range between 20 % and 25 % a second tier with additional 20 devices can be performed, such that the total number of values is 30.

The first criterion makes sense, although the value of 20 % is debatable. Assuming a normal distribution with a standard deviation σ, this means that 20 % deviation from label claim corresponds to 1.645 σ.

The second criterion is statistically incomprehensible. There is no σ-value, for which the probability of a measured dose-value is zero. The probability becomes very small for 3 or 4 or 5 σ.

The second tier is to salvage the batch; if there was an outlier in the first tier. However, increasing the number of samples increases the probability that there is a value outside ±25 %. Therefore the probability that a batch-is rejected increases with the number of samples.

It would be more sound statistically to decide about acceptance of a batch on the basis of the standard deviation. Outliers influence the standard deviation greatly, but a single outlier does not necessarily lead to a rejection of the batch. On the other hand by increasing the sample size the standard deviation is more accurately measured. Therefore it might be beneficial to increase the sample size in order to come to a statistically more relevant decision. The sample sizes could be defined as presently with 10 and in case of a too large standard deviation by additional 20 samples. If the standard deviation is then still too large, the batch has to be rejected. To a probability of 90 % of the values between ±20 % corresponds a standard deviation of 12 %.

Section III.F.1.h Spray Content Uniformity (SCU) Through Container Life, Lines 449-474

Concerning the acceptance criteria refer to comments on section III.F. 1 .g.

The requirement of the individual means of the beginning and end being between 85%-115% should be changed to the mean of all the samples measured per canister. The mean of the population is then based on a statistical sub-sample. Note that the mean of a sub-sample is not expected to conform to the specification for the mean of the population.

Section III.F.1.i Spray Pattern and Plume Geometry

Studies of spray pattern and plume geometry are appropriate for early product development studies to determine the appropriate valve and mouthpiece design. These development studies are used to determine the appropriate dimensions and other physical control criteria for the components. Control of components with appropriate sampling plans and dimensional measurements is far more precise than measuring spray pattern measurements. Spray pattern and plume geometry measurements are redundant and generally ineffective procedures to control component parameters. These parameters should be removed from the list of specifications for the drug product.

Section III.F.1.j Droplet Size Distribution

A requirement for a complex multi-stage droplet size control is not supported by the pharmaceutical or medical literature or by scientific rationale. We are not aware of clinical studies that have demonstrated that droplet size is in any way related to clinical safety or efficacy. As stated in the preceding section, control-of the pump or pump sub-components with an end-product test is redundant and possibly the least effective means of controlling product quality. 'Control of components with appropriate sampling plans and dimensional measurements is far more precise than measuring droplet size.

In addition, the setting of multi-stage droplet size specifications is open-ended and arbitrary since there is no body of scientific information on which to base meaningful specifications.

Section III.F.1.k Particle Size Distribution (Suspensions) Lines 517-518

"For suspension nasal sprays, the specification should include controls for the particle size distribution of the drug substance particles in the formulation."

The meaning of the term "in the formulation" is unclear. The Guidance should be revised to delete this test as a drug product specification, Alternatively, the particle size measurement could be performed in the suspension bulk solution, and incorporated into the in-process controls discussed in Section III.E. - Methods of Manufacture and Packaging (lines 3 16-3 19).

Section III.F.1.l. – Microscopic Evaluation Lines 525-536

This test is relatively crude in measurement capability, is subjective and is non-specific. Microscopy may be used in the early stages of product design and development to confirm other product characterization findings such as crystal growth in suspension MDIs. However, particle size, morphology, and agglomeration are better controlled by other test methods. The Guidance should be revised to state that in most cases microscopy as a routine control procedure is subjective and insensitive and should be avoided as a method for routine quality control.

Section III.F.1.m – Foreign Particulates Lines 538-544

The Guidance should be revised to delete the foreign particulates test. Foreign particulates is considered a GMP issue. It is controlled via sterile processing, filtration or other process controls, as demonstrated in the process validation.

Section III.F.1.n. - Microbial Limits
Lines 548-557

The Guidance should be revised to clarify that the microbial challenge test is a one-time development study, and that microbial testing is conducted on stability at 12-month intervals during development stability and on release only as a routine control procedure.

Section III.F.1.o. -Preservative Effectiveness
Lines 559-566

The Guidance should be revised to delete the preservative effectiveness test from this section. Preservative effectiveness is a one -time development study, and routine control is maintained via the preservative assay test (section III.F. 1 .e). This approach is discussed in lines 129 1- 1294 of the Guidance (section IV.L.).

Section III.F.1.q –Leachables (Stability)
Lines 580-591

Control of leachables is more appropriate at the component or bulk material level rather than on the product. Correlation between component levels and product levels should be evaluated during development. In addition, if levels are consistently well below the threshold of any safety concern, such testing may be eliminated altogether. The Agency should resist the temptation to use leachables as a confirmation of composition or process compliance during manufacture of components or product, which falls more appropriately in the realm of cGMP.

Development studies plus a commitment to qualify the elastomeric component in the primary stability studies and to conduct an annual re-qualification of the elastomeric components should meet the need to delete leachable testing as part of release testing and the annual stability protocol.

Section III.F.2. – Inhalation Solutions, Suspensions, and Sprays
Section III.F.2.a. – Appearance, Color and Clarity

See Comment to Section III.F.1.a

Section III.F.2.b. - Identification

See Comment to Section III. F. 1. b

Section III.F.2.c. – Drug Content (Assay)
Lines 615-617

Please revise the sentence regarding semipermeable container closure systems to clarify that the Agency requests that Assay be monitored both on a concentration basis and per container.

Section III.F.2.d. - Impurities and Degradation Products

See Comment to Section III.F.1.d

Section III.F.2.g. – Preservative Effectiveness

See Comment to Section III.F.1.o

Section III.F.2.h. – Foreign Particulates

See Comment to Section III.F.1.m

Section III.F.2.1. - Leachables (Stability)

See Comment to Section III.F.1.q

Section III.F.2.m. - Particle Size Distribution (Suspensions)

See Comment to Section 111. F. 1. k

Section III.F.2.n. - Microscopic Evaluation (Suspensions)

See Comment to Section III. F.1.l

Section III.F.2.o. - Pump Delivery for Inhalation Sprays

See Comment to Section III. F. 1 .f

Section III.F.2.p - Spray Content Uniformity (SCU) for Inhalation Sprays

See Comment to Section III.F. I .g

Section III.F.2.q - Spray Content Uniformity (SCU) Through Container Life for Inhalation Sprays (Device-Metered)

See comment on section III.F. 1.h

Section III.F.2.r. - Plume Geometry for Inhalation Sprays

See Comment to Section III.F.1.i

Section III.F.2.s - Particle/Droplet Size Distribution for Inhalation Sprays Lines 717-788

The guidance has prescribed these test parameters in a manner which is scientifically unsound and which diminishes the ability of the test method to control the product

Pump delivery is intended to control pump performance and spray content uniformity controls the quantity of drug delivered. Particle size by cascade impactor (CI) is intended to measure the. distribution of particle sizes. Acceptable variations in pump delivery can cause shifts in the amount of material deposited on the individual stages. By attempting to perform a full mass balance for each CI measurement and reporting CI results as a percent of label claim, particle size, pump delivery, and spray content uniformity data are confounded. As a result, critical information regarding the particle size distribution of the product is masked by variations in pump delivery and the corresponding product specifications become ambiguous. Therefore the guideline should permit correction of the CI results to account for permitted variations in pump performance.

The reporting of particle size distributions as a percent of label claim is superficially attractive in giving the appearance of a measure of the fine particle dose that is received by the patient. Studies have demonstrated that the cascade impactor is not an anthropomorphic simulator of the human respirator system. The CI is a device used to measure aerodynamic particle size distribution. The apparatus was initially designed for environmental analysis and later adapted for the testing of pharmaceutical aerosol products. When properly qualified, validated, and controlled, the apparatus is capable of measuring changes in the particle size distribution for a specified product. CI data for other purposes for which the significance has not been validated in an implicit or explicit manner is scientifically unsound and misleading.

The Guidance should be revised such that the mass balance of the CI system is determined as part of method validation and robustness studies. The criteria of 85% and 115% of label claim for total mass of drug collected on all stages and accessories should be taken as a system suitability condition and not as a specification. The 85% to 115%. mass balance criteria should also be changed to the 75% to 125% criteria in USP general chapter <601> Aerosols and in Pharrn. Eur 3rd Ed. Suppl. 1999 Monograph 671. In addition, environmental controls for CI measurements should be based on the evaluation of the method robustness data.

Any acceptance criteria must be consistent with how the test procedure is performed. If the procedure involves an average of multiple shots delivered into the test platform, then the range of 85 to 115 percent of label claim is consistent with the allowable range of drug delivery results. If the procedure is based on a single shot determination, then the range should be broadened to reflect the limits allowed for an individual shot, i.e., 75 to 125 percent.

Similarly, the distribution of drug on individual plates could be determined as an early product development study and the individual stages could then be grouped in an

appropriate way so as to control the particle size during routine testing. The particle size distributioncan then be measured via the relevant physically pooled stages. This would provide an opportunity to improve the method precision and possibly reduce the number of actuations needed to define a sample.

Section III.G. Container Closure Systems

Line 796

We suggest that the words "clinical efficacy" be replaced with "administered dose", so that the sentence reads ***"The administered dose of nasal and inhalation spray drug products is directly dependent on the design, reproducibility, and performance characteristics of the container closure system."***

Lines 812-815

"For device-metered nasal or inhalation spray drug products designed for use with replaceable reservoirs, the device should be specific for the intended formulation reservoir only and should not allow use of an alternate reservoir that contains a different formulation."

In the absence of data indicating otherwise, it is unclear that the potential risks of interchange associated with replaceable reservoirs and devices constitutes a compelling position to warrant a requirement for specificity between reservoirs and devices.

The risk that a patient would inadvertently interchange formulations within devices can be adequately minimized with appropriate directions for use and product specific identification.

The Guidance should be revised to instruct the sponsor to investigate and incorporate adequate measures to facilitate accurate replacement procedures through appropriate directions for use, training and readily identifiable product specific labeling.

The Guidance should set standards both for current products and for future products based on new, innovative technologies. The specifics for implementing these standards should be developed and justified by the innovator company on a product-by-product basis.

Lines 833-839

The Guidance discussion should be expanded to clarify which criteria will be required to demonstrate equivalency. An innovator may demonstrate a correlation between drug product leachables and the component extractables profile, and establish routine component controls only. In this case, there will be no acceptance criteria established for drug product leachables, and further guidance is needed for the ANDA applicant.

Terminology
"Control Extraction Studies"
Lines 859-942

The term "Control Extraction Studies" should be revised and clarified throughout the Guidance. We recommend replacing the term "Control Extraction Studies" with the term "Development Extraction Studies".

Lines 891-896
This section describes the process of conducting product characterization studies, which occurs during product development. The first line should be modified to clarify the purpose of these studies, which is to obtain the quantitative extraction profiles for elastomeric or plastic packaging components. At this stage acceptance criteria for the extractables profiles are not yet set.

Lines 893-894
"to establish acceptance criteria for each of the extractables from the container, closure and critical components (emphasis added) of the pump used.. . ."

We do not agree with the implication that a component, which is critical mechanically for the overall performance of the device, but which does not contact the formulation or the patient, be subject to "control extraction" (development extraction) studies. "Control extraction" studies should only be required for those critical components which contact either the formulation or the patient.

Line 908
". . . identify ***and quantify each extractable and establish appropriate acceptance criteria."***

Without the appropriate guidance, reporting levels for organic extractives will be driven to lower and lower levels, driven by advances in analytical technology, rather than relevant patient safety concerns. A general reporting limit for organic semi-volatile extractives, not including PNA's, nitrosamines, or other known toxicologically significant compounds, should be established. This level should be chosen based on amounts which are generally amenable to qualitative identification by chromatography combined with mass spectrometry. A reporting limit of 1 – 10 ppm is recommended.

Lines 914-915
"A rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the extractable profile(s)."

Specifications on the extractive profiles of elastomer and plastic components should be based on component manufacturing capability (subject to the above reporting limit), and set to ensure lot to lot consistency of extractives. The toxicological assessment should focus on the safety of extractives levels actually observed in drug product, manufactured with these components.

Section III.G.3. – Routine Extraction
Lines 932-933

"An extraction test should be performed on every incoming component batch using water and other suitable solvents.. ."

Please delete 'water and other suitable solvents' and replace it with the phrase 'a **suitable solvent'.** While the need for employing several solvent systems in order to fully characterize potential packaging component extractives during product development is accepted, the requirement for multiple solvent testing during routine control is burdensome and adds little value. Routine extraction. tests should be designed by selecting a solvent system which produces an extractives profile similar to the drug product. The use of routine extraction tests with multiple solvent systems which produce measurable but irrelevant extraction profiles do not enhance or protect product quality.

Lines 931 to 937
The option of employing gravimetric tests for the routine control of components should also be permitted with inhalation solution products, when development extraction studies demonstrate that a component does not contribute to the leachables profile of the drug product.

In the Guidance, please replace the term "determine the individual and total extractables" with the term "extraction profile", as defined in the finalized May 1999 ***Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics***, section II. A.

Line 940
The validation criteria listed are not consistent with ICH Guideline Q2A and Q2B. The Guidance should be revised to recognize ICH guidance for method validation.

Section III.G.4. -Acceptance Criteria
Line 970

We propose an additional sentence at the end of the section:
"Alternatively, for plastic components, specifications for extractables profiles on resin may be established instead of components if a correlation can be demonstrated between the extractables profiles of resin and finished components."

Section III. H. – Drug Product Stability

Line 978

The Guidance should be revised to address the topic of the submission of numerical data. In particular, the Guidance should adopt the ICH practices of reporting stability and other analysis data with respect to the QL/DL of the applicable method.

Section III.H.1. – Content of Stability Protocol
Lines 982-1006

The Guidance requires revision to clarify the content and purpose of the "protocol" and the "stability report". The information included under protocol in section III.H.1 includes excessive detail such as 'Statistical analysis approaches and evaluation for NDAs', 'Content and format of stability data' and 'Expiration Dating Period'. No guidance is provided regarding the "stability report" where such information is normally provided.

Section III.H.1.a. - Test Parameters, Acceptance Criteria, and Procedures

Line 1014
Content Uniformity should also be a listed exception to the stability test parameters required. Hopefully this is a simple omission; it is general practice to perform it as a release test only. The Guidance should reference the ICH Q6A guideline.

Section III.H.1.b. - Test Intervals
Lines 1022-1025

"Long-term test intervals (. . .), accelerated test intervals of a minimum of four test time-points for 6 months (e.g., 0, I, 3, 6 months) and intermediate test intervals (...) should be included."

It is requested that the Guidance change ***'(four"*** to ***"three test time-points",*** delete '1 month' in the brackets dealing with 'accelerated test intervals', and delete the request that intermediate test intervals ***"should be included".*** ICH Guideline Q1A 'Stability Testing of New Drugs and Products' should be applied. Approaches that are optional but are not required in the Q1A guideline should be referenced and deleted from this Guidance. Alternatively, the exact wording of the final draft text for the proposed Q1A update which describes alternative approaches may be used.

Section III.H.1.c - Container Storage Orientation
Line 1037
Please insert ***'Stability studies or one-time stability studies should include...etc.***' in the sentence ***'Stability studies should include . ..etc.***'

Please clarify that the storage orientation does not have to be studied on stability for all types of drug products, for example, unit dose vials.

Section III.H.1.d. - Test Storage Conditions
Lines 1048-1051
The Guidance should revise the wording that "the test storage conditions.. . should include.. . (2) intermediate (30±2°C/60±5 % RH), if applicable . . .". The ICH Guideline Q 1 A 'Stability Testing of New Drugs and Products' indicates specifically when testing

should be conducted at the intermediate storage condition. In cases when no "significant change" has occurred, such intermediate storage condition testing is not necessary.

Lines 1057-1062

The Guidance should revise the wording of the requirement that drug products packaged in semipermeable containers be studied under long term 25±2°C/40±5 % RH conditions. The final draft text for the proposed update of ICH 'Guideline. Q1 A 'Stability Testing of New Drugs and Products' indicates that this&rage condition is not necessary, and describes an alternative approach (deriving the'water loss through calculation). It is requested that the Guidance either references 'the Q1 A guideline or adopts the exact wording of this acceptable alternative approach.

Lines 1064-1070

The Guidance should justify the requirement for first three post approval batches to be tested to more than Room Temperature conditions as part of the post approval stability protocol. As long as product scale batches are used for the primary stability batches, the requirement to test the first three batches at environmental condition beyond the room temperature condition appears to be a change in Agency policy. It may be known that a product will fail at 6 months 40°C / 75% RH, and appropriate labeling restrictions are implemented. However, stability failures only at room temperature should affect the approved expiry period.

Lines 1094 - 1102

We agree that the report on stability studies should identify the batches of the drug substance used to manufacture the drug product batches. Identification information on the batches typically includes the batch number, synthetic method, synthesis site, etc. However, we do not agree that the stability report should present the "quality and purity of the drug substance" batches. The analytical profiles for the drug substance batches (including purity results) are presented elsewhere in the application. We recommend that the Guidance be revised to make this clear.

The same comments apply to the excipient batches.

Section III.H.1.g. - Sampling Plans and Statistical Analysis Approaches and Evaluation
Lines 1104-1107

This section is inadequate concerning analysis and evaluation of data and presumably the presentation of findings.

Section III.H.1.i - Expiration Dating Period
Line 1121

'The expiration dating period should be based upon full shelf-life stability studies...etc.'

The term "full shelf-life" should be revised. At the time of NDA submission the proposed expiration dating period should be determined based on a scientific evaluation of both real-time data and accelerated test data.

Section III.H.2. - Other Stability Considerations
Lines 1337 to 1352

The Guidance should be revised to remove the superficial discussion of changes in manufacturing process, materials, or sites. More detailed information is required and should be provided in a separate document patterned on the current SUPAC Guidance.

The validity of bracketing and matrixing has been demonstrated and accepted for stability testing of pharmaceutical products (see ICH Guideline Q1A ***Stability Testing of New Drug Products).*** No justification is provided as to why the Agency would arbitrarily disallow these approaches in this Guidance. The Guidance should be amended to accept bracketing and matrixing in stability studies of these drug products.

Section IV. - Drug Product Characterization Studies

The opening paragraph for this section states, "for the most part, these are one-time studies, usually performed on three batches of drug product.. .". There is no basis for selecting three batches for every study. In some case, one batch may be sufficient and the Guideline should be amended to so state. The term "optimum performance properties" is vague and subjective and should be revised to state "performance properties". Products are designed such that their performance properties support the product labeling.

Section IV.A Priming/Repriming in Various Orientations

This section should be revised to distinguish between nasal spray and inhalation spray drug products. Although it is appropriate for inhalation sprays, it is excessively detailed for nasal sprays.

Section IV.C. – Temperature Cycling
Lines 11951210

The guidance is silent on the justification for cycling for 28 days which exposes the product to either 84 or 112 cycles, Also note that the guidance should read three 8-hour cycles or four 6-hour cycles per day. The recommended repeated cycling conditions are far more aggressive than any variations that may be encountered during normal shipping and handling. It is not clear how test results obtained for samples stored at these conditions can be interpreted without an understanding of the underlying science.

Additionally, some of the listed test parameters are not relevant for a stress temperature cycling study (e.g., sterility, droplet size distribution, clarity.. .).

Section IV.D - In Vitro Dose Proportionality
Line 1213

Please insert the phrase **'(suspensions only)'** after ***'For nasal and inhalation spray drug products.. .'***. The problem of compaction of active ingredient in the dosing chamber with reduced dispersion pertains to suspensions, but is not applicable for solutions.

Section IV.F. - Device Ruggedness
Line 1222-1235

The Guidance should be revised to replace the term ***'the life of the device'*** with ***'the nominal number of sprays of the device',*** to clarify how the product performance is controlled.

Section IV.H. - Effect of Varying Flow Rates
Line 1249

"The total volume should be limited to 2 liters."

Please replace ***'limited to two liters'*** by ***'limited to*** 4 ***liters'*** for consistency with USP 1995, 10th Supplement, General chapter <601>. [Remark: 'two liters' should be allowed with justification.]

Section IV.I. - Profiling of Sprays Near Container Exhaustion
Line 1261-1270

The term "each individual spray" should be revised to "each individual dose".

Section IV.L - Preservative Effectiveness and Sterility Maintenance
Line 1299

The phrase ***"maintenance of sterility through the life of the reservoir during use"*** should be revised. The product properties can be only studied under the conditions described in the product labeling and instructions to patient.

IV.M. Characterization of Nebulizer Specified in the Labeling
Lines 1303-1305

As discussed in comments for Section II.B. (lines 71-72), this section of the Guidance should be deleted.

Section IV.O. – Stability of Primary (Unprotected) Package
Lines 13151323

"Drug products both newly manufactured and near the end of the proposed expiration dating period should be evaluated."

Please add the sentence ***"The evaluation data near the end of the proposed expiration dating period can be submitted after the NDA based on a commitment."***

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4b Express Freight Service *Packages over 150 lbs.*
Delivery commitment may be later in some areas

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